

2749 East Parleys Way, Suite 100 Salt Lake City, UT 84109 CLIA ID: 46D1077919

Extended Genetic Panel Created for:

Patient:

HIPAA Compliant Fax:

Physician:

Address:

Collection Date:

Specimen Type:

Key Test Findings

Accession #:

Gender:

DOB:

Received Date:

Report Generated:

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Pharmacogenetic Results

Assa	y Results	Phenotype	Clinical Consequences
ABCG2	421C>A CC	Normal Transporter Function	Consistent with a normal ABCG2 transporter function. The patient risk for statin-induced adverse events is normal.
ANKK1/DR	D2 DRD2:Taq1A AG	Altered DRD2 function	Consistent with a reduced dopamine receptor D2 function.
COMT	Val158Met GG	High COMT Activity	Consistent with a normal catechol O-methyltransferase (COMT) function.
CYP1A2	*1D/*1K	Intermediate Metabolizer - Possible Inducibility	Consistent with a slightly reduced CYP1A2 activity in absence of inducing substances. Rapid Metabolism occurs in presence of inducers such as barbiturates, cruciferous vegetables, carbamazepine, rifampin and smoking.
CYP2B6	*1/*22	Rapid or Normal Metabolizer	Consistent with typical or increased CYP2B6-mediated drug metabolism. Potential risk for side effects or loss of efficacy with drug susbtrates.
CYP2C19	*1/*1	Normal Metabolizer	Consistent with a typical CYP2C19 activity. This test did not identi risks for side effects or loss of efficacy with drug substrates.
CYP2C9	*2/*2	Poor Metabolizer	Consistent with a significant deficiency in CYP2C9 activity. Increased risk for side effects or loss of efficacy with drug substrates.
CYP2D6	*4/*4	Poor Metabolizer	Consistent with a significant deficiency in CYP2D6 activity. Increased risk for side effects or loss of efficacy with drug substrates.
CYP3A4	*1/*1	Normal Metabolizer	Consistent with a typical CYP3A4 activity. Caution is advised whe prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
CYP3A5	*3/*3	Poor Metabolizer	Consistent with a poor CYP3A5 activity. Caution is advised when prescribing narrow therapeutic index drugs. Alternative drugs or dose adjustment may be required if CYP3A inhibitors or inducers are co-prescribed.
OPRM1	A118G AA	Normal OPRM1 Function	Consistent with a normal OPRM1 receptor signaling efficiency induced by exogenous opioids. This is associated with a good analgesia following standard opioid doses and a poor response to naltrexone.
SLCO1B1	521T>C TT	Normal Transporter Function	Consistent with a typical SLCO1B1 transporter function. The patient's risk for statin-induced myopathy is not increased.
UGT2B15	*1/*1	Normal Metabolizer	Consistent with a typical UGT2B15 glucuronidation function. This test did not identify risks for side effects with drug substrates.
VKORC1	-1639G>A A/A	High Warfarin Sensitivity	VKORC1 is the site of action of warfarin. The patient may require substantial decrease in warfarin dose.
	Ca	rdiovascular/Thrombo	sis Risk Management
Gene	e Genotype	Phenotype	Clinical Consequences
Factor II Factor V Le	20210G>A GG eiden 1691G>A GG	No Increased Risk of Thrombosis	Unless other genetic or circumstantial risk factors are present, the patient is not expected to have an increased risk for thrombosis.
MTHFR MTHFR	1298A>C AC 677C>T CT	Increased Risk of Hyperhomocysteinemia	The patient has a significantly reduced MTHFR function leading to mild to moderate hyperhomocysteinemia. This appears to be associated with an increased risk for venous thromboembolism.

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✓	Apolipoprotein E	ε3/ε3	71	The patient has a normal APOE genotype and unless other genetic or circumstantial risk factors are present, the risk for hyperlipidemia/atherosclerotic vascular disease is not increased.

Cardiovascular/Thrombosis Risk Management

Thrombophilia

No Increased Risk of Thrombosis

Unless other genetic and/or circumstantial risk factors are present (ex: smoking, obesity...), estrogen-containing contraceptive and hormone replacement therapy can be used by the patient.

Myperhomocysteinemia

Increased Risk of Hyperhomocysteinemia

Testing total plasma homocysteine level may be beneficial. Hyperhomocysteinemia can be treated with nutritional supplementation.

✓ Hyperlipidemia/Atherosclerotic Cardiovascular Disease

No increased risk of hyperlipidemia/atherosclerotic vascular disease

No action is needed when a patient in normolipidemic.

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Medication Guidance		
	Psychotropic Medications	
Standard Precautions	Use With Caution	Consider Alternatives
Amphetamine (Adderall) Citalopram (Celexa) Clobazam (Onfi) Desvenlafaxine (Pristiq) Dexmethylphenidate (Focalin) Dextroamphetamine (Dexedrine) Diazepam (Valium) Escitalopram (Lexapro) Gabapentin (Neurontin) Lisdexamfetamine (Vyvanse) Lorazepam (Ativan) Methylphenidate (Ritalin) Mirtazapine (Remeron) Oxazepam (Serax) Paliperidone (Invega) Pregabalin (Lyrica) Sertraline (Zoloft)	Aripiprazole (Abilify) Atomoxetine (Strattera) Bupropion (Wellbutrin) Clozapine (Clozaril) Donepezil (Aricept) Duloxetine (Cymbalta) Fosphenytoin (Cerebyx) Galantamine (Razadyne) Iloperidone (Fanapt) Naltrexone (Vivitrol) Olanzapine (Zyprexa) Paroxetine (Paxil) Perphenazine (Trilafon) Phenytoin (Dilantin) Pimozide (Orap) Tetrabenazine (Xenazine) Vortioxetine (Brintellix)	Amitriptyline (Elavil) Clomipramine (Anafranil) Desipramine (Norpramin) Doxepin (Silenor) Haloperidol (Haldol) Imipramine (Tofranil) Nortriptyline (Pamelor) Risperidone (Risperdal) Thioridazine (Mellaril) Trimipramine (Surmontil) Venlafaxine (Effexor)
	Cardiovascular Medications	
Standard Precautions	Use With Caution	Consider Alternatives
Atorvastatin (Lipitor) Clopidogrel (Plavix) Irbesartan (Avapro) Lovastatin (Mevacor) Nebivolol (Bystolic) Pitavastatin (Livalo) Prasugrel (Effient) Pravastatin (Pravachol) Propranolol (Inderal) Rosuvastatin (Crestor) Simvastatin (Zocor) Ticagrelor (Brilinta)	Carvedilol (Coreg) Flecainide (Tambocor) Fluvastatin (Lescol) Mexiletine (Mexitil) Propafenone (Rythmol) Timolol (Timoptic) Warfarin (Coumadin)	Metoprolol (Lopressor)
, , ,	Pain Medications	
Standard Precautions	Use With Caution	Consider Alternatives
Buprenorphine (Butrans, Buprenex) Carisoprodol (Soma) Cyclobenzaprine (Flexeril, Amrix) Dihydrocodeine (Synalgos-DC) Fentanyl (Actiq) Hydromorphone (Dilaudid, Exalgo) Meperidine (Demerol) Oxymorphone (Opana, Numorphan) Tapentadol (Nucynta)	Celecoxib (Celebrex) Flurbiprofen (Ansaid) Hydrocodone (Vicodin) Methadone (Dolophine) Morphine (MS Contin) Oxycodone (Percocet) Piroxicam (Feldene) Tizanidine (Zanaflex)	Codeine (Codeine) Tramadol (Ultram)
	Other Medications	
Standard Precautions Dexlansoprazole (Dexilant) Esomeprazole (Nexium) Fesoterodine (Toviaz) Lansoprazole (Prevacid) Mirabegron (Myrbetriq) Omeprazole (Prilosec) Ondansetron (Zofran) Pantoprazole (Protonix) Rabeprazole (Aciphex) Tacrolimus (Prograf) Voriconazole (Vfend)	Use With Caution Darifenacin (Enablex) Glimepiride (Amaryl) Glipizide (Glucotrol) Glyburide (Micronase) Metoclopramide (Reglan) Tamsulosin (Flomax) Tolbutamide (Orinase) Tolterodine (Detrol)	Consider Alternatives

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Test Details

Gene	Alleles Tested
ABCG2	421C>A, 376C>T
ANKK1/DRD2	DRD2:Taq1A
Apolipoprotein E	ε2, ε4
COMT	Val158Met
CYP1A2	*1C, *1D, *1F, *1K, *1L, *1V, *1W
CYP2B6	*4, *5, *6, *8, *9, *11, *18, *22, *28
CYP2C19	*2, *3, *4, *4B, *5, *6, *7, *8, *9, *10, *12, *17
CYP2C9	*2, *3, *4, *5, *6, *8, *10, *11, *12, *13, *15, *25, *27
CYP2D6	*2, *3, *4, *4M, *6, *7, *8, *10, *11, *12, *14A, *14B, *15, *17, *18, *19, *20, *29, *35, *38, *41, *44, *56, *5 (gene deletion), XN (gene duplication)
CYP3A4	*1B, *2, *3, *6, *12, *17, *22
CYP3A5	*1D, *2, *3, *3C, *5, *6, *7, *8, *9
Factor II	20210G>A
Factor V Leiden	1691G>A
MTHFR	1298A>C
MTHFR	677C>T
OPRM1	A118G
SLCO1B1	*5, *15
UGT2B15	*2
VKORC1	1542G>C, -1639G>A, 1173C>T

Methodology:

Testing is performed on DNA extracted from a buccal swab. Samples are genotyped using Taqman® allele discrimination assays. The assays detect alleles listed above, including all common and most rare variants with known clinical significance at analytical sensitivity and specificity >99%.

Limitations:

The interpretations provided in this report are provided to assist health care providers, but they are not a treatment recommendation. Diagnosis and treatment remain the sole responsibility of the ordering physician. While the polymorphisms tested are important, other variants and mutations in these genes will not be detected. Mutations in other genes that could affect drug metabolism will not be detected. Non-genetic factors also affect metabolism. This test is not a substitute for clinical and therapeutic drug monitoring. This report does not address patient drug allergies or drug-drug interactions.

Date: 6/25/2014

Signature:

Kenneth Ward M.D.

CLIA FDA Statement:

This Laboratory Developed Test was developed and its performance characteristics determined by Affiliated Genetic, Inc. The laboratory is regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) as qualified to perform high-complexity clinical testing and has established and verified the test's accuracy. This test has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. These results are adjunctive to an ordering physician's diagnosis.

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Appendix: Dosing Guidance

Amitriptyline (Elavil)

Increased Sensitivity to Amitriptyline (CYP2D6 *4/*4 Poor Metabolizer)

Select an alternative drug or consider prescribing amitriptyline at a reduced dose (50% reduction) with monitoring of plasma concentrations of amitriptyline and nortriptyline.

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Aripiprazole (Abilify)

Increased Sensitivity to Aripiprazole (CYP2D6 *4/*4 Poor Metabolizer)

Aripiprazole dose should initially be reduced to one-half (50%) of the usual dose and then adjusted to achieve a favorable clinical response. Reduce the maximum dose to 10 mg/day (67% of the maximum recommended daily dose). The dose of aripiprazole for poor metabolizers patients who are administered a strong CYP3A4 inhibitor should be reduced to one-quarter (25%) of the usual dose.

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Atomoxetine (Strattera)

Increased Sensitivity to Atomoxetine (CYP2D6 *4/*4 Poor Metabolizer)

Careful titration is recommended with monitoring for toxicity until a favorable response is achieved. In children and adolescents up to 70 kg body weight, atomoxetine should be initiated at standard dosing of 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated. In children and adolescents over 70 kg body weight and adults, atomoxetine should be initiated at standard dosing of 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

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Bupropion (Wellbutrin)

Decreased Response to Bupropion (ANKK1 DRD2:Taq1A AG Altered DRD2 function)

Smoking Cessation: The patient's genotype is associated with a positive response to nicotine replacement therapy and a lesser response to bupropion treatment.

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Carvedilol (Coreg)

Moderate Sensitivity to Carvedilol (CYP2D6 *4/*4 Poor Metabolizer)

Carvedilol can be prescribed at standard label recommended-dosage and administration. CYP2D6 poor metabolizers may experience dizziness during up-titration. Careful titration is recommended with monitoring until a favorable response is achieved.

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Celecoxib (Celebrex)

High Sensitivity to Celecoxib (CYP2C9 *2/*2 Poor Metabolizer)

Consider starting at half the lowest recommended dose and evaluate response the first week. Be alert to gastrointestinal adverse events. Consider alternative medication for the management of Juvenile Rheumatoid Arthritis.

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Clomipramine (Anafranil)

Increased Sensitivity to Clomipramine (CYP2D6 *4/*4 Poor Metabolizer)

Consider alternative or prescribe clomipramine at 50% of recommended standard starting dose. Monitor plasma concentrations of clomipramine and desmethylclomipramine and titrate accordingly until a favorable response is achieved.

Clozapine (Clozaril)

Possible Sensitivity/Non Response to Clozapine (CYP1A2 *1D/*1K Intermediate Metabolizer - Possible Inducibility)

The patient may have high plasma drug levels at usual doses which may lead to higher adverse events. Dose reduction and careful titration is recommended until a favorable response is achieved. Smoking cessation may increase plasma drug levels leading to adverse events and therapeutic drug monitoring accompanied by dose reduction is recommended in patients who have quit smoking.

Codeine (Codeine)

Non-Response to Codeine (CYP2D6 *4/*4 Poor Metabolizer)

Greatly reduced morphine levels are expected and the patient may not experience adequate pain relief when taking codeine. Avoid prescribing codeine and consider alternative opioids other than tramadol or consider a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: Fentanyl, Morphine, Hydromorphone, Oxymorphone and Tapentadol.

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Darifenacin (Enablex)

Possible Sensitivity to Darifenacin (CYP2D6 *4/*4 Poor Metabolizer)

Darifenacin exposure is increased 30% in CYP2D6 poor metabolizers. Although no dose adjustment may not be needed in these patients, monitor patients for increased side effects when darifenacin is prescribed at standard label recommended-dosage and administration.

Desipramine (Norpramin)

Increased Sensitivity to Desipramine (CYP2D6 *4/*4 Poor Metabolizer)

Consider alternative or prescribe desipramine at 50% of recommended standard starting dose. Monitor plasma concentrations of desipramine and metabolites and titrate accordingly until a favorable response is achieved.

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Donepezil (Aricept)

Possible Altered Response to Donepezil (CYP2D6 *4/*4 Poor Metabolizer)

When compared to a normal metabolizer, a poor metabolizers has a 30% decrease in donepezil clearance; the clinical significance of this decrease is not well documented. Consider using a standard dosing regimen and be alert for adverse events and adjust dosage in response to clinical response and tolerability.

Doxepin (Silenor)

Increased Sensitivity to Doxepin (CYP2D6 *4/*4 Poor Metabolizer)

Consider alternative drug or reduce doxepin starting dose by 50%. Adjust maintenance dose according to nordoxepin plasma concentrations.

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Duloxetine (Cymbalta)

Possible Sensitivity to Duloxetine (CYP2D6 *4/*4 Poor Metabolizer)

Limited data suggest that duloxetine plasma concentrations might be increased in poor metabolizers of CYP2D6, therefore duloxetine can be prescribed at standard label recommended-dosage and careful titration is recommended until a favorable response is achieved.

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Flecainide (Tambocor)

Significantly Increased Sensitivity to Flecainide (CYP2D6 *4/*4 Poor Metabolizer)

Consider prescribing a lower flecainide dose. When compared to a CYP2D6 normal metabolizer, a poor metabolizer may require a 50% dose reduction. Careful titration with ECG recording and monitoring of flecainide plasma concentrations are recommended until a favorable clinical response is achieved.

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Flurbiprofen (Ansaid)

High Sensitivity to Flurbiprofen (CYP2C9 *2/*2 Poor Metabolizer)

At standard dosge, plasma concentrations of flurbiprofen are expected to be high resulting in an increased risk of toxicity. Administer flurbiprofen with caution and reduce dose if necessary.

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Fluvastatin (Lescol)

Increased Sensitivity to Fluvastatin (CYP2C9 *2/*2 Poor Metabolizer)

Increased fluvastatin plasma concentrations due to reduced CYP2C9 activity may occur, resulting in myotoxicity/hepatotoxicity. Consider monitoring the patient for treatment-related adverse effects and adjust dose as needed. Other adverse events predisposing factors include advanced age (≥65), diabetes, hypothyroidism, renal or hepatic impairments, high statin dose, CYP2C9 inhibitors, ABCG2 inhibitors and female gender.



Fosphenytoin (Cerebyx)

High Sensitivity to Fosphenytoin (CYP2C9 *2/*2 Poor Metabolizer)

Consider a standard loading dose and reduce maintenance dose by 50%. Evaluate response and serum concentrations after 7-10 days. Be alert to neurological concentration-related adverse events.



Galantamine (Razadyne)

Possible Sensitivity to Galantamine (CYP2D6 *4/*4 Poor Metabolizer)

A CYP2D6 poor metabolizer has a drug exposure that is approximately 50% higher than the exposure in a normal metabolizer. Although, dosage adjustment is not necessary in a patient identified as a CYP2D6 poor metabolizer as the dose of drug is individually titrated to tolerability, a slower titration can be considered as it may improve tolerability.

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Glimepiride (Amaryl)

Possible Sensitivity to Glimepiride (CYP2C9 *2/*2 Poor Metabolizer)

Subjects with reduced CYP2C9 activity may have increased glimepiride plasma drug concentrations at standard doses leading to hypoglycemic episodes. Because there is insufficient data to whether such changes have a significant clinical impact, glimepiride can be prescribed according to standard label recommended-dosage and administration with frequent monitoring of glucose plasma levels.



Glipizide (Glucotrol)

Possible Sensitivity to Glipizide (CYP2C9 *2/*2 Poor Metabolizer)

Subjects with reduced CYP2C9 activity may have increased glipizide plasma drug concentrations at standard doses leading to hypoglycemic episodes. Because there is insufficient data to whether such changes have a significant clinical impact, glipizide can be prescribed according to standard label recommended-dosage and administration with frequent monitoring of glucose plasma levels.



Glyburide (Micronase)

Possible Sensitivity to Glyburide (CYP2C9 *2/*2 Poor Metabolizer)

Subjects with reduced CYP2C9 activity may have increased glyburide plasma drug concentrations at standard doses leading to hypoglycemic episodes. Because there is insufficient data to whether such changes have a significant clinical impact, glyburide can be prescribed according to standard label recommended-dosage and administration with frequent monitoring of glucose plasma levels.

Haloperidol (Haldol)

Increased Sensitivity to Haloperidol (CYP2D6 *4/*4 Poor Metabolizer)

Consider alternative drug or prescribe haloperidol at 50% of the usual starting dose and then adjust dosage to achieve a favorable clinical response. Be alert to increased haloperidol plasma concentrations.



Hydrocodone (Vicodin)

Possible Altered Response to Hydrocodone (CYP2D6 *4/*4 Poor Metabolizer)

Decreased conversion of hydrocodone to the more active metabolite hydromorphone is expected in CYP2D6 poor metabolizers. However, there is insufficient evidence as to whether poor metabolizers have decreased analgesia when taking hydrocodone. Adequate pain relief can be achieved by increasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 may also be considered (i.e. morphine, oxymorphone, buprenorphine, fentanyl, methadone and hydromorphone).



lloperidone (Fanapt)

Increased Sensitivity to Iloperidone (CYP2D6 *4/*4 Poor Metabolizer)

lloperidone dose should be reduced by one-half and titrate slowly to avoid orthostatic hypotension. Because iloperidone is associated with QTc prolongation, caution is warranted when prescribing the drug in patients with reduced CYP2D6 activity. If patients taking iloperidone experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring.



Imipramine (Tofranil)

Increased Sensitivity to Imipramine (CYP2D6 *4/*4 Poor Metabolizer)

Consider alternative drug or consider a 50% reduction of imipramine recommended starting dose and then titrate in response to imipramine and desipramine plasma concentrations.



Methadone (Dolophine)

Possible Altered Response to Methadone (CYP2B6 *1/*22 Rapid or Normal Metabolizer)

Based on preliminary evidence, methadone plasma concentrations may be lower than those observed in normal metabolizers, which may result in inadequate therapeutic response. Methadone can be prescribed at standard label recommended-dosage. Monitor the patient response and adjust dose accordingly.

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Metoclopramide (Reglan)

Increased Sensitivity to Metoclopramide (CYP2D6 *4/*4 Poor Metabolizer)

Metoclopramide is metabolized at a slower rate in CYP2D6 poor metabolizers; this results in significantly higher serum concentrations of the drug. Considering the CNS and extrapyramidal adverse effects of metoclopramide, close monitoring for toxicity and eventually a dose decrease are recommended. Patients with renal disease at increased risk.

Metoprolol (Lopressor)

Significantly Increased Sensitivity to Metoprolol (CYP2D6 *4/*4 Poor Metabolizer)

Based on the genotype result, this patient is at risk of experiencing excessive beta-blockade when taking metoprolol at standard dosage. <u>Heart Failure</u>: Consider alternative beta-blockers such as bisoprolol or carvedilol or prescribe metoprolol at a lower dose. When compared to a normal metabolizer, a poor metabolizer may require 75% dose reduction. <u>Other indications</u>: Consider alternative beta-blockers such as bisoprolol or atenolol or prescribe metoprolol at a lower dose. When compared to a normal metabolizer, a poor metabolizer may require 75% dose reduction. If metoprolol is prescribed, be alert to adverse events (e.g. bradycardia, cold extremities).



Mexiletine (Mexitil)

Significantly Increased Sensitivity to Mexiletine (CYP2D6 *4/*4 Poor Metabolizer)

Consider prescribing a lower mexiletine dose. A slow titration with ECG recording and monitoring of mexiletine plasma concentrations are recommended until a favorable clinical response is achieved.

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Morphine (MS Contin)

Altered Response to Morphine (COMT Val158Met GG High COMT Activity)

The patient does not carry the COMT Val158Met mutation. The patient may require higher doses of morphine for adequate pain control. Dosing regimen needs to be individualized for each patient, taking into account the patient's prior analgesic treatment experience.



Naltrexone (Vivitrol)

Altered Response to Naltrexone (OPRM1 A118G AA Normal OPRM1 Function)

Treatment of alcohol dependence: the patient's has the wild-type genotype for OPRM1 that is associated with a poorer outcome with naltrexone therapy. Naltrexone-treated patients not carrying the 118A> G mutation, are less likely to respond to this drug and may have higher relapse rates than those who are carriers of this mutation.

Mortriptyline (Pamelor)

Increased Sensitivity to Nortriptyline (CYP2D6 *4/*4 Poor Metabolizer)

Select an alternative drug or consider prescribing nortriptyline at a reduced dose (50% reduction) with monitoring of plasma concentrations of nortriptyline and metabolites.



Olanzapine (Zyprexa)

Possible Sensitivity/Non Response to Olanzapine (CYP1A2 *1D/*1K Intermediate Metabolizer - Possible Inducibility)

There is little evidence regarding the impact of CYP1A2 genetic variants on olanzapine response. Smokers may be at risk for non-response at standard doses. Careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels leading to adverse events and therapeutic drug monitoring accompanied by dose reduction may be needed in patients who have quit smoking.



Oxycodone (Percocet)

Possible Altered Response to Oxycodone (CYP2D6 *4/*4 Poor Metabolizer)

Decreased conversion of oxycodone to the more active metabolite oxymorphone is expected in CYP2D6 poor metabolizers. However, there is insufficient evidence as to whether poor metabolizers have decreased analgesia when taking oxycodone. Adequate pain relief can be achieved by increasing the dose in response to pain symptoms. Other opioids not metabolized by CYP2D6 may also be considered (i.e. morphine, oxymorphone, buprenorphine, fentanyl, methadone and hydromorphone).



Paroxetine (Paxil)

Possible Sensitivity to Paroxetine (CYP2D6 *4/*4 Poor Metabolizer)

At standard label-recommended dosage, paroxetine levels are expected to be high. Careful titration is recommended until a favorable response is achieved. When compared to a CYP2D6 normal metabolizer, a poor metabolizer may require a 50% dose reduction.

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Perphenazine (Trilafon)

Increased Sensitivity to Perphenazine (CYP2D6 *4/*4 Poor Metabolizer)

Patients with a decreased CYP2D6 function will eliminate perphenazine more slowly which can result in higher drug concentrations and possibly higher adverse events (extrapyramidal symptoms). Consider close monitoring and dose reduction to avoid toxicity.

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Phenytoin (Dilantin)

High Sensitivity to Phenytoin (CYP2C9 *2/*2 Poor Metabolizer)

Consider a standard loading dose and reduce maintenance dose by 50%. Evaluate response and serum concentrations after 7-10 days. Be alert to neurological concentration-related adverse events.



Pimozide (Orap)

Increased Sensitivity to Pimozide (CYP2D6 *4/*4 Poor Metabolizer)

The pimozide concentrations observed in poor CYP2D6 metabolizers are expected to be high and the time to achieve steady state pimozide concentrations is expected to be long (approximately 2 weeks). Consequently, CYP2D6 poor metabolizers are at an increased risk of QT prolongation at standard doses of pimozide. In CYP2D6 poor metabolizers, pimozide doses should not exceed 4 mg/day in adults or 0.05 mg/kg/day in children, and doses should not be increased earlier than 14 days.

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Piroxicam (Feldene)

High Sensitivity to Piroxicam (CYP2C9 *2/*2 Poor Metabolizer)

At standard dosge, plasma concentrations of piroxicam are expected to be high resulting in an increased risk of toxicity. Administer piroxicam with caution and reduce dose if necessary.

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Propafenone (Rythmol)

Increased Sensitivity to Propafenone (CYP2D6 *4/*4 Poor Metabolizer)

Consider reducing the propafenone dose and monitor ECG. Compared to normal metabolizers, poor metabolizers may require a 70% dose reduction. Consider monitoring for plasma concentrations.

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Risperidone (Risperdal)

Significantly Increased Sensitivity to Risperidone (CYP2D6 *4/*4 Poor Metabolizer)

Consider alternative drug or prescribe risperidone at a reduced dose and be extra alert of adverse events and adjust dosage in response to clinical response and tolerability.

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Tamsulosin (Flomax)

Increased Sensitivity to Tamsulosin (CYP2D6 *4/*4 Poor Metabolizer)

Tamsulosin is metabolized at a slower rate in CYP2D6 poor metabolizers; this results in significantly higher serum concentrations of tamsulosin. Therefore, this drug should be used with caution in patients known to be CYP2D6 poor metabolizers, particularly at a daily dose higher than 0.4 mg.



Tetrabenazine (Xenazine)

Increased Sensitivity to Tetrabenazine (CYP2D6 *4/*4 Poor Metabolizer)

Individualization of dose with careful weekly titration is required. The first week's starting dose is 12.5 mg daily; second week, 25 mg (12.5 mg twice daily); then slowly titrate at weekly intervals by 12.5 mg to a tolerated dose. **The maximum daily dose in CYP2D6 poor metabolizers is 50 mg with a maximum single dose of 25 mg.** If serious adverse events occur, titration should be stopped and the dose of tetrabenazine should be reduced. If the adverse event(s) do not resolve, consider withdrawal of tetrabenazine.

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Thioridazine (Mellaril)

Increased Sensitivity to Thioridazine (CYP2D6 *4/*4 Poor Metabolizer)

Reduced cytochrome CYP2D6 activity results in elevated plasma levels of thioridazine and would be expected to augment the prolongation of the QTc interval associated with thioridazine and may increase the risk of serious, potentially fatal, cardiac arrhythmias, such as Torsades de pointes type arrhythmias. Such an increased risk may result also from the additive effect of coadministering thioridazine with other agents that prolong the QTc interval. Therefore, thioridazine is contraindicated in patients with reduced levels of CYP2D6 activity.

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Timolol (Timoptic)

Increased Sensitivity to Timolol (CYP2D6 *4/*4 Poor Metabolizer)

Potentiated systemic beta-blockade (e.g., bradycardia) has been reported during timolol treatment by patients with decreased CYP2D6 activity. Monitor patient for treatment-related adverse effects.



Tizanidine (Zanaflex)

Possible Sensitivity/Non Response to Tizanidine (CYP1A2 *1D/*1K Intermediate Metabolizer - Possible Inducibility)

There is little evidence regarding the impact of CYP1A2 genetic variants on tizanidine response. Smokers may be at risk for non-response and may require higher doses. There is an association between high tizanidine plasma concentrations and the risk of hypotension and excessive sedation, therefore careful monitoring is recommended during dosing adjustment. Smoking cessation may increase plasma drug levels leading to excessive hypotension and sedation. Careful monitoring accompanied by dose reduction may be needed in patients who have guit smoking.



Tolbutamide (Orinase)

Possible Sensitivity to Tolbutamide (CYP2C9 *2/*2 Poor Metabolizer)

Subjects with reduced CYP2C9 activity may have increased tolbutamide plasma drug concentrations at standard doses leading to hypoglycemic episodes. Because there is insufficient data to whether such changes have a significant clinical impact, tolbutamide can be prescribed according to standard label recommended-dosage and administration with frequent monitoring of glucose plasma levels.



Tolterodine (Detrol)

Possible Sensitivity to Tolterodine (CYP2D6 *4/*4 Poor Metabolizer)

Tolterodine is metabolized at a slower rate in CYP2D6 poor metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of its active metabolite (5-hydroxymethytolterodine). Considering the antimuscarinic potency of tolterodine and its active metabolite and the protein binding of these compounds, tolterodine accounts for the major part of the clinical effect in poor metabolizers and the same dosage can be applied irrespective of phenotype status.

Patients with Congenital or Acquired QT Prolongation: The effect of tolterodine on the QT interval prolongation is greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and is more pronounced in CYP2D6 poor metabolizers than normal metabolizers. This should be considered when tolterodine is prescribed to patients with a known history of QT prolongation or patients who are taking Class IA or Class III antiarrhythmics.

Tramadol (Ultram)

Non-Response to Tramadol (CYP2D6 *4/*4 Poor Metabolizer)

The patient will not experience adequate pain relief when taking tramadol. Avoid prescribing tramadol and consider alternative opioids other than codeine or consider a non-opioid analgesic such as a NSAID or a COX-2 inhibitor. Unless contraindicated, available alternative opioids not sensitive to CYP2D6 function include: Fentanyl, Morphine, Hydromorphone, Oxymorphone and Tapentadol.

Trim

Trimipramine (Surmontil)

Increased Sensitivity to Trimipramine (CYP2D6 *4/*4 Poor Metabolizer)

Consider alternative drug or consider a 50% reduction of trimipramine recommended starting dose and then titrate in response to trimipramine plasma concentrations.

Venlafaxine (Effexor)

Significantly Increased Sensitivity to Venlafaxine (CYP2D6 *4/*4 Poor Metabolizer)

The patient has an increased risk of experiencing side effects when taking standard doses of venlafaxine. Consider alternative drug or prescribe venlafaxine and be extra alert of adverse events and adjust dosage in response to clinical response and tolerability. Monitor O-desmethylvenlafaxine plasma concentrations.

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Vortioxetine (Brintellix)

Increased Sensitivity to Vortioxetine (CYP2D6 *4/*4 Poor Metabolizer)

CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carboxylic acid metabolite, and CYP2D6 poor metabolizers of CYP2D6 have approximately twice the vortioxetine plasma concentration of normal metabolizers. **Vortioxetine starting dose should be reduced by one-half. The maximum recommended dose is 10 mg/day in known CYP2D6 poor metabolizers.** Consider 5 mg/day for patients who do not tolerate higher doses.



Warfarin (Coumadin)

Very High Sensitivity to Warfarin (CYP2C9 *2/*2 VKORC1 -1639G>A A/A)

Initiation Therapy: The expected therapeutic **dose is substantially lower than the usual one.** Consider using the following warfarin dose range provided in the FDA-approved label: **0.5-2 mg/day.** OR consider using a personalized dose as calculated by the provided pharmacogenetic algorithm. The estimated time to reach steady-state is more than 2-4 weeks. Frequent INR monitoring is recommended.

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Prescription Alert

DOB

This individual has been tested for gene variants that may affect medications prescribed.

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GENE	ABCG2	Normal Transporter Function	
	ANKK1	Altered DRD2 function	
	COMT	High COMT Activity	
	CYP1A2	Intermediate Metabolizer - Possible Inducibility	
	0)/D0D0		
	CYP2B6	Rapid or Normal Metabolizer	
	CYP2C19	Normal Metabolizer	5
	CYP2C9	Poor Metabolizer	l ji
	CYP2D6	Poor Metabolizer	RESULT
	CYP3A4	Normal Metabolizer	
	CYP3A5	Poor Metabolizer	
	OPRM1	Normal OPRM1 Function	
	SLCO1B1	Normal Transporter Function	
	UGT2B15	Normal Metabolizer	
	VKORC1	High Warfarin Sensitivity	

Healthcare Providers: For up-to-date information concerning the impact of these genetic tests on drug precribing by may consult the PharmGKB database:

www.pharmgkb.org

Note:This patient has also been tested for common variants in the Factor II, Factor V, MTHFR, and ApoE genes.These results are available on the patient's medical records.

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